

## **Mn-SOD Upregulation by Electroacupuncture Attenuates Ischemic Oxidative Damage via CB1R-Mediated STAT3 Phosphorylation**

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**Background:** Electroacupuncture (EA) pretreatment elicits the neuroprotective effect against cerebral ischemic injury through cannabinoid receptor type 1 receptor (CB1R). The current study aims to investigate whether the signal transducer and activator of transcription 3 (STAT3) and manganese superoxide dismutase (Mn-SOD) were involved in the EA pretreatment through CB1R.

**Methods:** At 2 h after EA pretreatment, focal cerebral ischemic injury was induced by transient middle cerebral artery occlusion for 60 min in C57BL/6 mice. The expression of Mn-SOD in the penumbra was assessed by western-blot and immunofluorescent staining at 2 h after reperfusion. In the presence or absence of Mn-SOD siRNA, the neurological deficit score, the infarct volume, the TUNEL staining, and oxidative stress were evaluated. Furthermore, the Mn-SOD protein expression and phosphorylation of STAT3 at 705Y were also determined in the presence and absence of CB1R antagonists (AM251, SR141716) and CB1R agonists (ACEA, WIN 55,212-2).

**Results:** EA pretreatment upregulated the Mn-SOD protein expression and Mn-SOD positive neuronal cells at 2 h after reperfusion. EA pretreatment also attenuated oxidative stress, inhibited cellular apoptosis, and induced neuroprotection against ischemic damage whereas these beneficial effects of EA pretreatment were reversed by knockdown of Mn-SOD. Mn-SOD upregulation and STAT3 phosphorylation by EA pretreatment was abolished by two CB1R antagonists while pretreatment with two CB1R agonists increased the expression of Mn-SOD and phosphorylation level of STAT3.

**Conclusion:** Mn-SOD upregulation by EA attenuates ischemic oxidative damage through CB1R-mediated STAT3 phosphorylation in stroke mice, which may represent one new mechanism of EA pretreatment-induced neuroprotection against cerebral ischemia.

**Keywords:** cerebral ischemia; electroacupuncture; manganese superoxide dismutase (Mn-SOD); oxidative damage; cannabinoid CB1 receptor; signal transducer and activator of transcription 3 (STAT3)